Is It Time to Return to Cholesterol Goals for Optimal Patient Management?

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IF THE RULES DON’T WORK, CHANGE THEM

Disclosures

Speaker Bureau: AstraZeneca, Amarin, Merck, Sanofi, Genzyme
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Heart healthy lifestyle habits are the foundation of ASCVD prevention in individuals not receiving cholesterol-lowering drug therapy, recalculate estimated 10-y ASCVD risk every 4-6 yr in individuals aged 40-75 y without clinical ASCVD or diabetes and with LDL-C 70-189 mg/dL.

**ASCVD Statin Benefit Groups**

- Age ≤75 y
  - High-intensity statin
    - Moderate-intensity statin if not candidate for high-intensity statin
- OR
  - if not candidate for high-intensity statin
    - Moderate-intensity statin
- Clinical ASCVD
  - High-intensity statin
    - Moderate-intensity statin if not candidate for high-intensity statin
  - LDL-C ≥190 mg/dL
  - Moderate-intensity statin
- Diabetes
  - Type 1 or 2
  - Age 40-75 y

**Definitions of High- and Moderate-Intensity Statin Therapy**

- **High**: Daily dose lowers LDL-C by approx ≥50%
- **Moderate**: Daily dose lowers LDL-C by approx 30% to 50%

**Monitoring Statin Adherence and Therapeutic Response**

- Follow-up 4-12 wk
- Reinforce medication adherence
  - Reinforce adherence to intensive lifestyle changes
  - Exclude secondary causes of hypercholesterolemia
- Anticipated therapeutic response?
  - Less-than-anticipated therapeutic response
    - Follow-up 4-12 wk and thereafter as indicated
    - Reinforce improved adherence
    - Increase statin intensity
    - OR
      - Consider addition of nonstatin drug therapy
  - Anticipated therapeutic response?
    - Reinforce continued adherence
    - Follow-up 3-12 mo

**Indicators of anticipated therapeutic response and adherence to selected statin intensity**

- • High-intensity statin therapy reduces LDL-C approx ≥50% from the untreated baseline
- • Moderate-intensity statin therapy reduces LDL-C approx 30% to <50% from the untreated baseline

**Intolerance to recommended dose of statin therapy**

- Assess medication and lifestyle adherence
- Fasting lipid panel

"It’s interpret-your-own-test-results day today."
Is It Time to Return to Cholesterol Goals for Optimal Patient Management?

- NO! Goals still recommended for targets LDL-C
- NO! Goals exist
  - Adherence
  - % Reduction
- Are these reasonable goals?

Case for Consideration

- John is a 45 year old white male, who eats a “heart healthy diet”, mostly lean meat, chicken and fish, whole grains, nuts, fruits, vegetables and skim dairy products
- He exercises 3 times a week at gym
- Travels for work extensively
- ETOH 2-3 times/week 1-2 drinks with meals mostly
- Non smoker
Case for Consideration

- Father died of sudden death/MI at age 64 complete LM occlusion on autopsy with extensive non-obstructive disease elsewhere. He had “high cholesterol” but unclear if was taking any lipid lowering medication and what his cholesterol values were.
- Mother alive and well
- No sibs
- John is married, with two children

Case for Consideration

- John is referred for “CV Risk evaluation” by his PCP given his fathers history
- John is overweight BMI 27, but lifts weights WC 41” He thinks if anything he is underweight
- BP 120/74 mmHg.
- FBS 105, HbA1c 5.9%
- Fasting Lipid Panel Tchol 220 mg/dL, HDLc 38 mg/dL, TG 240 mg/dL, LDL-C (calculated) 134
- Non-HDL-c 182
- Lp(a) 120 mg/dL

Case for Consideration

- ACC/AHA : 10 yr. ASCVD risk 1.8%, Lifetime risk is 45%
  - Additional risk factors to consider
    - LDL>160 (No)
    - Genetic dyslipidemia (unlikely)
    - Fam.Hx Premature CHD (no)
    - HS-CRP >2 (No)
    - CAC score >300 A Units or >75% for age (Not done)
    - ABI<0.9 Normal
    - Elevated Lifetime risk (yes)
- Goal ? Target ? Rx ?
Case for Consideration

- NLA Recommendations
  - Very High Risk
    - CHD, TIA, ABI < 0.9, AAA, Carotid Plaque >50% (NOS)
    - DM = 2 risk factors
  - High Risk
    - DM 1-2 Risk factors
    - DM 0-1 risk factor
    - CKD 3B or 4 (NOS)
    - LDL > 190, Non-HDL > 220 mg/dL
  - > 3 ASCVD Risk Factors (patient has 2)
    - Age M>45
    - Family History Premature CHD
    - Smoker
    - HTN
    - LDL > 100 mg/dL
  - Biomarkers (need one if 2 or more risk factors above)
    - CAC > 300 A units
    - CRP > 2
    - Lp(a) > 50
    - Ur alb or ratio > 30 mg/L
    - Lifetime risk > 45%

- Goal: LDL < 130 and Non HDL < 130 mg/dL, and Consider drug Rx. Non-HDL-C reduction 29% (moderate intensity statin) but (a) elevation and family history might necessitate more aggressive LDL lowering (+ Metabolic Syndrome)

What are we trying to prevent?

The Risk-Benefit Paradigm vs the Causal Exposure Paradigm: LDL as a primary cause of vascular disease

Peter F. Todo, MD, PhD, George Thanassoulis, MD, Ken Williams, Curt D. Furberg, MD, PhD, Allan Sniderman, MD

Journal of Clinical Lipidology (2014) 8, 594–605

Two Different Prevention Approaches
Two Different Perspectives

Circulation
The Recent National Lipid Association Recommendations: How Do They Compare to Other Established Dyslipidemia Guidelines?

Laura Fleck - James A. Underberg - Jonathan D. Novotna - Eugenia Caines

Similarities between the ACC/AHA Guideline and the NLA Recommendations

- Lipid screening for primary prevention is recommended at 5-year intervals
- Lifestyle therapy is advocated as first step in all treatment algorithms
- ASCVD risk reduction is the goal of therapy
- Moderate- or high-intensity statin therapy is the central focus of pharmacotherapy
- Patient-provider discussion of risk/benefit ratio precedes all decisions on drug treatment
- Regular lipid follow-up is warranted to assess adherence to therapy

Observational Epidemiologic Cohort Study of 2146 Patients with FH and no CHD at Baseline

Kaplan-Meier curve estimates of cumulative coronary heart disease-free survival among patients with Familial hypercholesterolemia according to statin treatment (P<0.001 for difference)
Genetic Studies

- Genetic epidemiology reduces the likelihood of confounding by focusing on single variables: genetic mutations
- Identification of specific mutations may serve to generate hypotheses for other types of trials
- Often limited in patient selection and costly

Data Demonstrating Genetic Variants Affecting ASCVD Risk

- Loss of function mutations in the gene encoding for PCSK9 (the serine protease responsible for lysosomal catabolism of the LDL receptor) are associated in Black subjects with 28% reduction in LDL-C and an 88% CHD relative risk reduction (p=0.008 for the reduction, 95% CI 0.02-0.81, p=0.03)
- Loss of function mutations in the gene encoding for NPC1L1 (the protein that facilitates proximal small intestinal absorption of cholesterol) are associated with a 12 mg/dl reduction in LDL-C and a 55% CHD relative risk reduction (p=0.04 for the reduction, 95% CI 0.25-0.67, p=0.008)


Distribution of Plasma LDL-Cholesterol Levels (Panel A) and Incidence of Coronary Heart Disease (Panel B) among Black Subjects, According to the Presence or Absence of a COLO or APOE Allele

28% lower LDL in carriers

88% CHD Risk Reduction

p=0.008

Association Between Presence of Inactivating Mutations in NPC1L1, Plasma Lipid Levels, and CHD Risk

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Mean Difference between Carriers and Noncarriers</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>-13</td>
<td>0.03</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>-12</td>
<td>0.04</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>2</td>
<td>0.29</td>
</tr>
<tr>
<td>Triglycerides (% change)</td>
<td>-12</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Odds ratio for CHD in mutation carriers vs noncarriers: 0.47 (95% CI 0.25−0.87; P = 0.008) on the basis of a meta-analysis of independent samples.

ACC/AHA Statin Benefit Groups

H=High-intensity statin, M= Moderate-intensity statin

- Clinical ASCVD (H preferred); M if age >75 or if not candidate for H).
- Primary elevations of LDL-C ≥190 mg/dl (H preferred); M if not candidate for H).
- Age 40-75 years with diabetes, and LDL-C 70-189 mg/dl, no clinical ASCVD (M if 10-year risk <7.5%; H if ≥7.5%).
- Age 40-75 years, no clinical ASCVD or diabetes, LDL-C 70-189 mg/dl, and estimated 10-year ASCVD risk ≥7.5% using Pooled Cohort Equations (M or H).

2013 ACC/AHA Guideline Additional Markers of Increased ASCVD Risk

- Consider for additional assessment of ASCVD risk in patients who do not fall into one of the 4 statin benefit groups (5-7.4% 10-year risk)
  - LDL-C ≥160 mg/dl
  - Family history premature ASCVD
  - CAC score ≥300 Agatston units or 75th %tile
  - Hs-CRP ≥2 mg/L
  - Ankle-brachial index <0.9
  - High lifetime risk @ age 20-59
ACC/AHA Perspective on Statin Therapy

- Statin intensity trials showed clear benefit for high-intensity versus moderate-intensity statins
- Because fixed doses, not dosage titrations, were employed, one should not assume that a dosage titration strategy is correct or that addition of non-statins to achieve low LDL-C is indicated

TNT: Treatment Effects on LDL-C

![Graph showing treatment effects on LDL-C](image)

Treating to New Targets (TNT) in Stable CHD Patients: LDL-C Results and Primary Endpoint

![Bar chart showing mean LDL-C values and patients with major CV event](image)
TNT 3 month on treatment LDL predicts mortality & ASCVD Events

Am J Cardiol 2007;100:747–752

Overview of the NLA Recommendations

1. All preventive therapy begins with risk assessment and a provider-patient discussion of the pros and cons of therapy
2. Lifestyle therapy is the first step in all ASCVD preventive recommendations, regardless of baseline risk
3. Judicious use of evidence-based drug therapy, particularly moderate and high dose statins, is associated with optimal ASCVD risk reduction
4. When excessive circulating atherogenic cholesterol (non-HDL-C [primary target] and LDL-C) persists after appropriate lifestyle and statin therapy, the use of non-statin therapy should be considered
5. Long-term follow-up fostered by provider-patient communication is essential for optimal ASCVD prevention

Association of LDL Cholesterol, Non–HDL Cholesterol, and Apolipoprotein B Levels With Risk of Cardiovascular Events Among Patients Treated With Statins

A Meta-analysis

Conclusion Among statin-treated patients, on-treatment levels of LDL-C, non-HDL-C, and apoB were each associated with risk of future major cardiovascular events, but the strength of this association was greater for non-HDL-C than for LDL-C and apoB.
Non-HDL-C vs LDL-C

What is the Advantage of Non-HDL-C over LDL-C in Assessing ASCVD Risk?

- Non-HDL-C is more predictive of ASCVD risk than LDL-C in observational studies. The same is true for on-treatment levels in clinical trials of statin therapy.
- When non-HDL-C and LDL-C are discordant, risk follows non-HDL-C.
- Non-HDL-C testing is universally available, requires no additional cost, and accurate values may be obtained in the non-fasting state.

NLA Recommendations: Stepwise Approach to Risk Assessment

1. Identify highest ASCVD risk category that applies to the patient
2. If very-high risk, begin with moderate- or high-intensity statin with non-HDL-C and LDL-C goals <100 and <70 mg/dL respectively
3. In remaining patients count number of major risk factors and treat to goals for non-HDL-C <130 and LDL-C <100 mg/dL respectively
Further Risk Assessment in Patients with Two Major Risk Factors

- Key Clinical Criteria
  - Multi-pack/day cigarette smoking; strong family history of premature CHD; non-HDL-C ≥190 mg/dL or LDL-C ≥160 mg/dL
- High Risk Quantitative Risk Scoring
  - 10-year FRS ≥10%; ACC/AHA 10-year risk ≥15%; lifetime risk ≥25%
- High Risk Biomarkers
  - CAC score ≥30 Agatston units or ≥75th %ile; hs-CRP ≥2.0 mg/L; Lp(a) ≥50 mg/dL (protein; isoform insensitive assay); or urine albumin/creatinine ratio ≥30 mg/g

NLA Perspective on Non-Statin Lipid Drug Therapy

- If non-HDL-C and LDL-C goals are not achieved with statin therapy, the addition of evidence-based non-statin therapy should be considered to lower atherogenic cholesterol levels and to achieve goals
  - Ezetimibe is a safe, evidence-based non-statin therapy that may be considered in post MI patients and selected other patients with elevated non-HDL-C and/or LDL-C
  - Resins or niacin may be considered in selected patients
  - Meta-analyses of fibrate therapy in subgroups with atherogenic dyslipidemia suggest ASCVD risk reduction

On-Treatment LDL-C and CHD Events in Primary Prevention

Data abstracted from original publications
Effect of PCSK9 Inhibitors on Cardiovascular Events: OSLER and ODYSSEY Long-Term

What’s the “Take Home”?

Lipid Guidelines in 2016: Common Ground
- Identify and treat patients in accordance with presumed ASCVD risk
- Exclude and address secondary causes
- Lifestyle intervention is always an important component of the initial management of dyslipidemia
- Engage patient in risk/benefit discussion if drug therapy is considered
- Employ evidence-based drug therapy for optimal ASCVD risk reduction
- Long-term lipid follow-up is the key to assessing patient adherence to therapeutic recommendations
Guidelines

• Venkman: I make it a rule never to get involved with possessed people.
• Actually, it’s more of a guideline than a rule...